DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

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A. B. Reddy, M.D.
Gastroenterology Consultants
of Tuscaloosa, P.C.
100 Rice Mine Road, NE, Suite E
Tuscaloosa, Alabama 35406

9958 '97 SEP 19 A9:38

Re: Docket No. 78N-036L
Comment No. CP13

Dear Dr. Reddy:

This letter concerns your above referenced citizen petition dated March 16, 1992, requesting the use of sorbitol in an oral dosage form for the management of constipation.

On December 5, 1994, the Office of OTC Drug Evaluation issued a letter to you (copy enclosed) stating that the agency finds that the data and information submitted to support the petition request are inadequate and providing the reasons for this finding. Accordingly, the petition is denied.

If you have any questions regarding the petition, please refer to the docket number above and submit all inquiries, in triplicate, to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Drive, Room 1-23, Rockville, MD 20857.

Sincerely yours,

Ronald G. Chesemore
Associate Commissioner
for Regulatory Affairs

Enclosure

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PDN6

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December 5, 1994

A. B. Reddy, M. D.
Gastroenterology Consultants
of Tuscaloosa, P. C.
100 Rice Mine Road, NE, Suite E
Tuscaloosa, Alabama 35406

Re: Docket No. 78N-036L
Comments No. CP13,
LET55, and MT7

Dear Dr. Reddy:

This is in further response to your citizen petition dated March 16, 1992, which was filed as CP13 under Docket No. 78N-036L on April 9, 1992. You requested the use of sorbitol in an oral dosage form for the management of constipation.

On May 5, 1992, I wrote (our code LET55) asking that you clarify whether you are seeking approval for sorbitol as an OTC or as a prescription drug. I also explained that the Advisory Review Panel concluded in its March 21, 1975 report and the agency concurred in the tentative final monograph of January 15, 1985 that sorbitol is safe and effective for OTC use in rectal enemas only. On May 21, 1992, you stated in a telephone conversation with Helen Cothran of my staff (our code MT7) that you were interested in pursuing OTC status of sorbitol for oral use under the OTC laxative monograph.

Your petition included two articles from the literature, both reporting the results of the same study. The study was conducted by Dr. Lederle, et al., at the VA hospital associated with the University of Minnesota. The double-blind, crossover, randomized study was done in 30 elderly men (65 to 80 years old) with chronic constipation. Lactulose and 70 percent sorbitol were each given for 4 weeks, with the objective of demonstrating that sorbitol is as effective as lactulose as a laxative. The study began with a 2-week phase-in period in which lactulose was given in a single-blind manner. This was followed by a 2-week wash-out period, the first treatment period, a second 2-week wash-out period, and then the second treatment period.

The subjects needed to have a history of more than 1 year of constipation in order to be eligible. Constipation was defined as a history of all of the following: less than three spontaneous bowel movements per week; less than one bowel movement per day if taking other laxatives; bowel movements associated with straining, hard stool, bloating, or sensation of incomplete evacuation. During each treatment phase, subjects were asked to take initially 30 milliliters (mL) (21 g sorbitol or 20 g lactulose) of the study laxative daily and then adjust

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the dose themselves to between 0 and 60 mL per day as needed. Subjects were instructed to maintain a high fiber diet and continue psyllium if they were already taking it. After recruitment, subjects were seen only at the end of the washout and treatment periods. During the treatment phases, subjects were to record the daily dose of the laxative used and to assess each bowel movement as being hard, normal, or loose. At the end of each treatment period, subjects were asked to mark on a visual analogue scale (100 mm) the "intensity" of constipation they felt during that treatment period. Side effects of each treatment period were compared using the average of the weekly symptom-scores total by adding the scores of all subjects for each symptom (bloating, cramp, flatulence, nausea, diarrhea, fecal incontinence, and "other") individually, using a scale where none=0, mild=1, moderate=2, and severe=3.

The investigators did a statistical analysis of all parameters by t-test and reported all were statistically insignificant except for nausea. There were no significant period effects for any outcomes measured, and no significant sequence effects for any outcome except for the average number of days per week with bowel movements ($p<0.001$). The average number of days per week with bowel movements for subjects in the sorbitol-lactulose sequence was 5.89 with sorbitol versus 6.15 with lactulose, and for subjects in the lactulose-sorbitol sequence was 4.46 with lactulose versus 4.57 with sorbitol. There was a significant difference between the two sequences but not between the treatments or periods. This sequence difference appears to reflect a difference at randomization between the two sequence groups rather than an interaction between treatment and period.

The authors noted the following problems with the studies:

1. The subjects were ambulatory older men; therefore, the study results may not be applicable to younger men, women, and people who are bedridden.

2. Some subjects were unable to participate because of gastrointestinal symptoms from lactulose prior to randomization. Similar problems are likely to occur with and limit the use of sorbitol.

3. Baseline stool data with subjects not taking laxatives were not collected prior to treatment and probably would be unobtainable because these subjects would not likely refrain from all laxatives for a prolonged period.

4. The study was not placebo-controlled. (Thus, it is difficult to conclude that sorbitol was truly effective in this study.)

In addition to the problems noted by the authors, we have the following specific comments:

1. Compliance to the study regimen was not measured. One follow-up during the entire 4-week period of each treatment is insufficient.

2. Only the average of the weekly summation scores of adverse effects of the two treatments was compared. A better way to measure would be to compare the number of subjects (rather than a summation score) experiencing a particular symptom during each treatment. The category of the ADR profile termed "Other" should be defined. Also, "Diarrhea," as a side-effect category, is difficult to define.

3. The fact that the average number of days per week for bowel movements has a highly significant sequence effect ($p<0.001$) indicates the possibility that the results are different for the two treatment periods. Under such a significant sequence effect, the test for treatment effect is generally statistically biased and not valid. This issue was not resolved in the published article.

4. The high fiber diet (and continued use of psyllium for those already taking this laxative) may have compromised the study results.

5. Inter- and intra-subject variability estimates have not been provided for the primary endpoints of this study to assess the adequacy of the size of the trial for clinical equivalence.

In conclusion, we find that the data and information submitted are insufficient to support OTC status of an oral dosage form of sorbitol for the management of constipation. Any comment you may wish to make on the above information should be submitted in three copies, identified with the docket number shown at the beginning of this letter, to the Dockets Management Branch (HFA-305), Food and Drug Administration, Room 1-23, 12420 Parklawn Drive, Rockville, MD 20857.

We hope this information will be helpful.

Sincerely yours,

William E. Gilbertson, Pharm. D.
Director
Monograph Review Staff
Office of OTC Drug Evaluation
Center for Drug Evaluation and Research